THE CLAIMS ARE UNOBVIOUS

Applicants assert that the Examiner has not met the burden of establishing a *prima facie* case of obviousness. A *prima facie* case of obviousness requires the Examiner to cite to references that (a) disclose all the elements of the claimed invention, (b) suggest or motivate one of skill in the art to combine or modify those elements to yield the claimed combination, and (c) provide a reasonable expectation of success should the claimed combination be carried out.[1] Failure to establish **any one** of these three requirements precludes a finding of a *prima facie* case and, without more, entitles Applicants to allowance of the claims at issue. The cited art fails to establish *prima facie* obviousness because the cited references do not teach all of the elements of the claimed invention, and there is no motivation to combine the cited art. Furthermore, even if such a combination were made, the cited does not teach or suggest every element of the presently claimed invention. Thus, Applicants assert that Claims 1, 2-29, and 31-54 are unobvious over the art cited by the Examiner.

I. There is No Motivation to Combine the References

Obviousness cannot be established by combining the teaching of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination.[2] Applicants assert that the cited references do not contain any suggestion for their combination.

The presently claimed invention provides methods for characterization of nucleic acid sequences and sequence changes using a cleavage means that recognizes **folded** nucleic acid **structure**.[3] This is in contrast to methods based on nucleic acid **sequence** (*e.g.*, PCR, Q-Beta replicase, Ligase Chain Reaction, Northern and Southern Blotting, and RNase Protection assays). As described in the specification (*See e.g.*, pages 1-13), there are many drawbacks and limitations to the methods based on nucleic acid sequences. For example, PCR efficiency

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[1] *See, e.g., Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990); and *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

[2] *In re Geiger*, 2 USPQ 2d 1276, 1278 (Fed. Cir. 1987).

[3] *See e.g.*, specification page 15, lines 24-27, stating that "[i]n one embodiment of the present invention, the treating step comprises rendering double-stranded nucleic acid substantially single-stranded, and exposing the single-stranded nucleic acid to conditions such that the single-stranded nucleic acid assumes a secondary or characteristic folded structure."

is limited by factors such as DNA length, secondary structure, and primer length and design.[4] Unlike PCR, the methods of the present invention do not require the use of primers (*i.e.*, sequence-recognition elements are not used) and benefit from secondary structure (*i.e.*, folded structures) of the sample nucleic acids. In contrast, PCR requires the use of primers, and secondary structure in the sample nucleic acid is detrimental to the reaction.

The Examiner argues that "[o]ne of ordinary skill in the art would have been motivated to combine the teachings of Lyamichev *et al.* with Young, Seela and Roling, and Young *et al.* to produce a method that could be used to optimize allele-specific PCR wherein the polymerase is also a single stranded endonuclease which recognized hairpin structures of the single stranded nucleic acid because Lyamichev *et al.* taught that this method could be used to optimize allele-specific PCR."[5] Applicants must respectfully disagree.

The Examiner has alleged one tenuous and minor point of commonality between Lyamichev *et al.* and Young, Seela and Roling, and Young *et al.* (*i.e.*, the one sentence reference to allele-specific PCR in the discussion of Lyamichev *et al.*). Here, Lyamichev *et al.* briefly mention using the unpaired primers of allele-specific PCR to act as pilot oligonucleotides to direct selective cleavage of unwanted templates. However, Young, Seela and Roling, and Young *et al.* **do not teach or suggest allele-specific PCR**. There is no teaching or suggestion in Young, Seela and Roling, or Young *et al.* of the discrimination between alleles in a PCR reaction. Thus, there is no justification for making this tenuous connection with Lyamichev *et al.*, and there is no motivation to combine Lyamichev *et al.* and Young, Seela and Roling, and Young *et al.*

Even if Young, Seela and Roling, or Young *et al.* related to allele-specific PCR, a point which the Applicants contest, there is no motivation to combine these references with Lyamichev *et al.*, with respect to the presently claimed invention. The present invention is not allele-specific PCR and is not even related to allele-specific PCR. As discussed above, the Examiner has alleged one tenuous and minor point of commonality between Lyamichev *et al.* and Young, Seela and Roling, and Young *et al.* (*i.e.*, the one sentence reference to allele-specific PCR in the discussion of Lyamichev *et al.*) and used this tenuous point to justify

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[4] *See e.g.*, Specification at page 6, lines 11-15.

[5] Office Action, page 6.

combining the references for all purposes (*i.e.*, combining teachings unrelated to allele-specific PCR). Combinations made by identifying minor points of commonality as a means of generally combining the references are improper when the context the references, taken as a whole, does not suggest or motivate such a combination. Courts have continuously emphasized that the references must be evaluated as a whole, so that their teachings are applied in the context of their significance to a technician at the time (*i.e.*, a technician without the Applicants' knowledge of the solution that is provided by the invention).[6]

The cited references, as a whole, do not support their combination by the Examiner. In fact, the tenuous point of commonality (*i.e.*, the reference to allele-specific PCR in Lyamichev *et al.*) *teaches away* from the present invention. Lyamichev *et al.* discuss using the unpaired primers of allele-specific PCR to act as pilot oligonucleotides to direct selective cleavage of unwanted templates. In contrast to the presently claimed invention, Lyamichev *et al.*, teach primer-directed cleavage (*i.e.*, a sequence-dependent detection method). As described above, the present invention does not require the use of primers (*i.e.*, is not a sequence-dependent method). Furthermore, the combination of Lyamichev *et al.* and Young, Seela and Roling, and Young *et al.* as related to allele-specific PCR, *teaches away* from the presently claimed invention, as primers are not employed for the cleavage of intra-strand structures. Thus, there is no motivation to combine the cited art, nor can the Examiner point to a motivation that would apply to the presently claimed invention. In addition, it is impermissible to combine references when the references teach away from the combination.[7]

Because allele-specific PCR teaches away from the present invention and because Young, Seela and Roling, and Young *et al.* do not teach or suggest either allele-specific PCR or the methods of the present invention, there can be no motivation to combine the cited references, and *prima facie* obviousness has not been established. Thus, Claims 1, 3-29, and 31-54 are allowable and Applicants respectfully request that this rejection be withdrawn.

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[6] *See e.g., Interconnect Planning Corp. v. Feil,* 227 USPQ 543, 551, 774 F.2d 1132, 1143 (Fed. Cir. 1985).

[7] *See e.g., In re Grasselli,* 713 F.2d 731, 218 USPQ 769, 779 (Fed. Cir. 1983).

II. The Cited References Do Not Teach or Suggest All of the Elements of the Present Invention.

Even if the cited references are combined, the combination of the cited references does not teach or suggest all of the elements of the presently claimed invention. Indeed, the Examiner has conceded that the primary reference, Lyamichev *et al.*, does not teach "a method for identifying strains of microorganisms, . . . that the detected cleavage products may be compared with cleavage products of nucleic acid structures from reference microorganisms, . . . that the nucleic acid may comprise a nucleotide analog, . . . that the PCR may be done with these nucleotide analogs or that the PCR primers were from ribosomal RNA . . . ."[8]

Furthermore, Lyamichev *et al.* do not teach or suggest that the 5' nuclease activity of DNA polymerases may be used to characterize sequence variation between nucleic acids by cleavage of **intra-strand** secondary structure.[9] In contrast, Lyamichev teaches the detection of nucleic acids by cleavage of one strand in a structure formed by **inter-strand** annealing (*i.e.*, between a target and a primer). Young, Seela and Roling, and Young *et al.* do not remedy the deficiencies of Lyamichev *et al.*, as these references only teach general methods of PCR, and do not teach methods for characterization of cleaved nucleic acids. In other words, these references teach the use of the synthetic activity of *Taq* polymerase, unlike the present invention which involves the cleavage activity of 5' nucleases. Thus, even if made, the Examiner's combination of Lyamichev *et al.*, and Young, Seela and Roling, and Young *et al.*, a combination which Applicants assert is improper, does not teach or suggest that the 5' nuclease activity of DNA polymerases may be used to characterize sequence variation between nucleic acids by cleavage of **intra-strand** secondary structure.

The Examiner's combination of the cited art is directed to "a method that could be used to optimize allele-specific PCR."[10] Allele-specific PCR involves the hybridization of a primer to target nucleic acid and does not provide intra-strand secondary structure. Thus, the Examiner's combination of Lyamichev *et al.*, and Young, Seela and Roling, and Young *et al.*

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[8] Office Action, pages 4-5.

[9] *See e.g.*, Claim 1, reciting "a nucleic acid substrate . . . " (emphasis added) and "treating said nucleic acid substrate under conditions such that said substrate forms one or more cleavage structures . . ."

[10] Office Action, page 6.

requires two or more nucleic acids, wherein secondary structure would confound the hybridization and effectiveness of allele-specific PCR (*i.e.*, the cleavage structures taught by the presently claimed invention are not compatible with the PCR methods of Young, Seela and Roling, and Young *et al.*). Thus, the combination of Lyamichev *et al.* with Young, Seela and Roling, and Young *et al.* does not teach or suggest all of the elements of the presently claimed invention, and *prima facie* obviousness has not been established. In view of the above arguments, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that Applicants' claims as amended should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (650) 299-8120.

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